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ORIGINAL ARTICLE

Case Control Study

TCF7L2 rs7903146 polymorphism is associated with gastric cancer: A case-control study in the Venezuelan population

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Abstract

AIM: To explore the association between *TCF7L2* rs12255372 and rs7903146 single nucleotide polymorphisms (SNPs) and gastric cancer risk in Venezuelan patients.

METHODS: We performed a case-control study including 122 paraffin-embedded archived intestinal-type gastric cancer samples and 129 biopsies obtained by superior endoscopy from chronic gastritis patients. Gastric cancer samples were classified according the degree of carcinoma differentiation. Genomic DNA was extracted from tissues, and the two SNPs of *TCF7L2* gene (rs12255372 and rs7903146) were genotyped by polymerase chain reaction-restriction fragment length polymorphism reactions. Multiple regression analysis with adjustments for age and gender were performed and best-fitting models of inheritance were determined.

Statistic powers were post-hoc calculated.

RESULTS: After adjusting for age and sex the *TCF7L2* rs7903146 TT genotype was associated with gastric cancer risk under the recessive genetic model (OR = 3.11, 95%CI: 1.22-7.92, *P* = 0.017). We further investigated the distribution of rs12255372 and rs7903146 genotypes according gastric cancer stratified by degree of differentiation, and we observed that carriers of rs7903146 T allele (CT + TT *vs* CC) had a significantly increased risk of moderate/well differentiated gastric cancer (dominant model, OR = 2.55, 95%CI: 1.35-4.80, *P* = 0.004), whereas the rs7903146 TT genotype was associated with poorly differentiated gastric cancer in the recessive model (OR = 3.65, 95%CI: 1.25-10.62, *P* = 0.018). We did not find association between rs12255372 SNP and the susceptibility of developing gastric cancer.

CONCLUSION: *TCF7L2* rs7903146 polymorphism is associated with gastric cancer risk in the Venezuelan population, and could be related to determine the degree of differentiation of tumor cells.

Key words: Gastric cancer; Wnt/β-catenin pathway; *TCF7L2*; Single nucleotide polymorphism; Genetic susceptibility

Core tip: TCF7L2 transcription factor plays an important role in transcriptional activation induced by the Wnt/β-catenin pathway, which is reported to be associated with human carcinogenesis and it is found activated in 30%-50% of gastric cancers. *TCF7L2* polymorphisms rs12255372 and rs7903146 are associated with a significant risk of type 2 diabetes and in the development of several types of cancer. This is the first report of association of these *TCF7L2* variants with the risk of gastric cancer. We conducted a case-control study including samples of Venezuelan patients in which the rs7903146 T allele was found associated with the risk of gastric cancer, suggesting its use as potential diagnosis biomarker in patients with this malignance.

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INTRODUCTION

The transcription factor 7-like 2 (*TCF7L2* or *TCF-4*) gene, is located on the long arm of chromosome 10q25.3[1]. Moreover, the TCF7L2 protein is a high mobility group box-containing transcription factor, which acts as an effector of the Wnt/β-catenin signaling pathway, therefore playing a pivotal role in cell development and growth regulation[2-4].

The TCF7L2 protein is also involved in blood glucose homeostasis, and their gene variants rs7903146 (C>T) and rs12255372 (G>T) [it is in high linkage disequilibrium (LD) with rs7903146] are among the most significant genetic factors influencing the risk for type 2 diabetes (T2DM)[5-7]. Although the specific role of TCF7L2 in the development of T2DM is still being investigated, evidence indicates that alterations in the Wnt signaling pathway affect insulin secretion through the reduction of the GLP-1 production[8,9]. Moreover, aberrant Wnt signaling is involved in the pathogenesis of numerous types of human cancers[10], and particularly to the development and progression of gastric cancer[11].

Although with contradictory conclusions, several studies have studied the association between *TCF7L2* rs7903146 and rs12255372 single nucleotide polymorphisms (SNP) with susceptibility to several types of cancer, including in the prostate, breast, colon, rectum, lung and ovary[11-21]. However, to the best of our knowledge, the participation of these SNPs in the susceptibility of gastric cancer has not been evaluated yet.

Here, we present a case-control study carried out to evaluate the role of rs7903146 and rs12255372 polymorphisms in the risk of gastric cancer in the Venezuelan population where gastric cancer is the leading cause of death due to cancer (http://www.mpps.gob.ve/).

MATERIALS AND METHODS

Subjects

A total number of 122 gastric cancer cases and 129 controls were included in this study. The group of cases consisted of paraffin-embedded intestinal-type gastric cancer samples according to Laurén's classification, which were obtained from the Pathology Department Service of the Hospital Antonio María Pineda (HAMP), Barquisimeto, Venezuela. Tumor samples were classified into well differentiated, moderately differentiated and poorly differentiated cancer depending on the degree of differentiation of the cancerous cells[22].

Patients diagnosed with chronic gastritis without evidence of gastric cancer constituted the control group. Chronic gastritis samples obtained from patients with criteria for indication of endoscopy (Gastroenterology Service of the HAMP) were evaluated according to the Sydney classification system in regard to the presence and degree of atrophic gastritis, granulocytic infiltration and lymphocytic infiltration. Two independent experts in pathology from the Department of Pathology (HAMP) evaluated all biopsies. The Bioethics Committee of the School of Health Sciences, Universidad Centroccidental

Table 1 Characteristics of the study population *n* (%)

Variables	Controls	Gastric cancer
Overall	129	122
Sex[a]		
Male	63 (48.8)	88 (72.1)
Female	66 (51.2)	34 (27.9)
Age[a], mean ± SD (yr)	58.81 ± 9.99	62.32 ± 14.29
Histological differentiation		
Well		14 (11.5)
Moderated		56 (45.9)
Poor		52 (42.6)

[a]$P < 0.05$ *vs* control.

Lisandro Alvarado (UCLA) approved this study, and all patients gave their written informed consent to participate in the study.

Genotyping

Genomic DNA was extracted from paraffin sections of patients' tissues by MagneSil® Genomic Fixed Tissue System (Promega, United States), and from endoscopic biopsies using the Wizard Genomic DNA Purification kit (Promega, United States) following the manufacturer's instructions.

SNPs genotyping was achieved by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. We designed primers to detect both polymorphisms using software DNAMAN version 7.212 (Lynnon Corporation) in order to amplify shorter DNA fragment, which resulted more efficient when DNA extracted from paraffin-embedded tissues was used as template. The primer sets included in the reactions to amplify the rs7903146 and rs12255372 polymorphisms were: forward 5'-ACAATTAGAGAGCTAAGCACTTTTTAGGTA-3'[23], reverse 5'-CTAAGTTACTTGCCTTCCCTG-3, and forward 5'-GAAAGTGTATTGCTATGTCCAG-3', reverse 5'-CAGAGGCCTGAGTCATTATCA-3', respectively.

PCR reactions were performed in 25 μL reaction volume containing 1-2 μL of genomic DNA, 1 × Green GoTaq® Flexi Buffer, 1.5 μmol/L $MgCl_2$, 0.2 μmol/L dNTPs, 0.6 μmol/L of each primer and 1.25 U of GoTaq DNA Polymerase (Promega, United States). The amplification conditions were: 3 min at 95 ℃; then 35 cycles of 20 s at 95 ℃, 30 s at 59 ℃ (for rs12255372)/ 57 ℃ (for rs7903146), and 30 s at 72 ℃; followed by a final extension cycle of 5 min at 72 ℃. To perform the allelic assignment PCR products were incubated at 37 ℃ overnight with a restriction enzyme, *Rsa*I (New England Biolabs, United States) for rs7903146 and *Tsp*509I (New England Biolabs, United States) for rs12255372. For rs7903146, the *Rsa*I enzyme produces two fragments of 81-bp and 29-bp with the C allele, whereas the T allele is not cleaved, and its PCR products remains of 110-bp. Fragments with the rs12255372 G allele are not cleaved and remains of the original size (119-bp), moreover, the T allele PCR product results in two fragments of 85-bp and 34-bp after incubating with *Tsp*509I enzyme. PCR products and restriction fragments were analyzed on 3% agarose gel electrophoresis with ethidium bromide staining. To validate the RFLP-PCR assays we randomly select 20% of the samples to carry out DNA nucleotide sequencing. Furthermore, 30 samples of each genotype were re-genotyped and a concordance of 100 was observed.

Statistical analysis

P values and ORs with 95%CI were calculated using multiple regression analysis adjusted by age and gender. A *P* value of < 0.05 was considered statistically significant when comparing differences among groups, and the analyses were carried out using the SPSS 11.0 package software (SPSS Inc., United States). We used two-sided χ^2 test to determine if genetic distributions were in Hardy-Weinberg equilibrium. The analysis for LD was estimated using the Arlequin software version 3.5.1.2. The comparisons of genotype distributions of polymorphisms were performed following the codominant, dominant and recessive inheritance models, taking into account known risk alleles. To determine the best-fitting models we used the Akaike information criterion (AIC). Post-hoc power analyses were calculated using G*Power software (version 3.1). A biomedical statistician from the UCLA performed statistical review of the study. All authors accessed the data of the study and agreed final version of the manuscript.

RESULTS

The characteristics of the cases and controls are summarized in Table 1. Gastric cancer tissues included 14 well- (11.5%), 56 moderately (45.9%), and 52 poorly (42.6%) differentiated carcinoma. As shown in Table 2, the genotype distributions of rs7903146 and rs12255372 SNPs in the control group were in Hardy-Weinberg equilibrium ($P > 0.05$). The differences between the groups with respect to the distribution by age and sex were significant; therefore we adjusted for these variables in the subsequent analyses of the relationship between polymorphisms and gastric cancer susceptibility. Rs7903146 and rs12255372 SNPs were in moderate LD ($D' < 0.644$; $r^2 < 0.33$). Among gastric cancer cases five samples did not amplify with the rs12255372 primer set.

The rs7903146 TT genotype was significantly associated with increased risk of gastric cancer under both the codominant (OR = 3.61, 95%CI: 1.36-9.61, $P = 0.01$) and the recessive model (OR = 3.11, 95%CI: 1.22-7.92, $P = 0.017$), after adjustment for age and gender (Table 2). However, the recessive model of inheritance was suggested as the best-fitting one by the AIC score.

Furthermore, we evaluated the genotype distribution of rs7903146 and rs12255372 SNPs in the

Table 2 Association of *TCF7L2* rs7903146 and rs12255372 polymorphisms with gastric cancer *n* (%)

SNP	Risk allele	HWE (control), *P* value	Inheritance model	Genotype	Control	Gastric cancer	OR (95%CI)[1]	*P* value[1]
rs7903146	T	0.741			*n* = 129	*n* = 122		
				CC	73 (56.6)	56 (45.9)	1	
			Codominant	CT	49 (38.0)	48 (39.3)	1.30 (0.75–2.25)	0.345
				TT	7 (5.4)	18 (14.8)	3.61 (1.36–9.61)	0.010
			Dominant	CC	73 (56.6)	56 (45.9)	1	
				CT + TT	56 (43.4)	66 (54.1)	1.58 (0.94–2.64)	0.082
			Recessive	CC + CT	122 (94.6)	104 (85.2)	1	
				TT	7 (5.4)	18 (14.8)	3.11 (1.22–7.92)	0.017
rs12255372	T	0.053			*n* = 129	*n* = 117		
				GG	85 (65.9)	78 (66.7)	1	
			Codominant	GT	35 (27.1)	32 (27.3)	1.06 (0.59–1.92)	0.841
				TT	9 (7.0)	7 (6.0)	1.11 (0.38–2.25)	0.849
			Dominant	GG	85 (65.9)	78 (66.7)	1	
				GT + TT	44 (34.1)	39 (33.3)	1.06 (0.61–1.83)	0.839
			Recessive	GG + GT	120 (93.0)	110 (94.0)	1	
				TT	9 (7.0)	7 (6.0)	1.02 (0.36–2.90)	0.972

[1]Adjusted by age and gender; Statistical power (1-β) was calculated for all observed *P* values. HWE: Hardy-Weinberg equilibrium; SNP: Single nucleotide polymorphism.

Table 3 Distribution of *TCF7L2* rs7903146 and rs12255372 single nucleotide polymorphisms according to the degree of histological differentiation of gastric cancer *n* (%)

SNP	Inheritance model	Genotype	Control	M/W GC	OR (95%CI)[1]	*P* value[1]	P GC	OR (95%CI)[1]	*P* value[1]
rs7903146			*n* = 129	*n* = 70			*n* = 52		
		CC	73 (56.6)	25 (35.7)	1		31 (59.6)	1	
	Codominant	CT	49 (38.0)	36 (51.4)	2.33 (1.20–4.51)	0.012	12 (23.1)	0.57 (0.26–1.23)	0.152
		TT	7 (5.4)	9 (12.9)	5.70 (1.60–20.3)	0.007	9 (17.3)	2.99 (0.99–8.92)	0.050
	Dominant	CC	73 (56.6)	25 (35.7)	1		31 (59.6)	1	
		CT + TT	56 (43.4)	45 (64.3)	2.55 (1.35–4.80)	0.004	21 (40.4)	0.88 (0.45–1.71)	0.708
	Recessive	CC + CT	122 (94.6)	61 (87.1)	1		43 (82.7)	1	
		TT	7 (5.4)	9 (12.9)	2.93 (0.99–8.68)	0.053	9 (17.3)	3.65 (1.25–10.6)	0.018
rs12255372			*n* = 129	*n* = 66			*n* = 51		
		GG	85 (65.9)	38 (57.6)	1		40 (78.4)	1	
	Codominant	GT	35 (27.1)	24 (36.3)	1.44 (0.39–5.36)	0.589	8 (15.7)	0.51 (0.21–1.21)	0.129
		TT	9 (7.0)	4 (6.1)	1.63 (0.83–3.21)	0.156	3 (5.9)	0.81 (0.20–3.26)	0.770
	Dominant	GG	85 (65.9)	38 (57.6)	1		40 (78.4)	1	
		GT + TT	44 (34.1)	28 (42.4)	1.58 (0.84–3.00)	0.158	11 (21.6)	0.56 (0.26–1.22)	0.145
	Recessive	GG + GT	120 (93.0)	62 (93.9)	1		48 (94.1)	1	
		TT	9 (7.0)	4 (6.1)	1.15 (0.33–4.05)	0.823	3 (5.9)	0.87 (0.22–3.43)	0.844

[1]Adjusted by age and gender; Statistical power (1-β) was calculated for all observed *P* values. W/M: Well and moderately differentiated gastric cancer; P GC: Poorly differentiated gastric cancer; SNP: Single nucleotide polymorphism.

gastric cancer samples divided according to the degree of histological differentiation of tumors (Table 3). To conduct these analyses, samples of well and moderately differentiated gastric carcinoma were gathered in a single group (57.4%; 70/122). Compared with CC genotype, rs7903146 CT heterozygous and TT homozygous genotypes, as well as the combined genotype CT + TT, had a significantly increased risk for moderate/well differentiated gastric cancer (ORs = 2.33, 5.70 and 2.55, respectively), adjusted by age and gender (Table 3).

Moreover, rs7903146 TT genotype was associated with poorly differentiated gastric cancer in the recessive model (OR = 3.65, 95%CI: 1.25-10.62, *P* = 0.018). However, in these analyses the AIC score suggested the dominant model (CT + TT *vs* CC) as the best-fitting one in the comparisons of gastritis samples with both groups of gastric cancer. Importantly, the post-hoc analysis revealed that the study has acceptable statistical power (1 - β > 0.80 at type I level of 0.05) to support the observed significant associations for rs7903146 genotypes. Finally, we did not identify any significant difference in genotype frequencies of rs12255372 SNP between gastric cancer and gastritis groups, even taking into account the degree of tumor differentiation (Tables 2 and 3).

DISCUSSION

Gastric cancer is a multifactorial disease that results

from the complex interplay of several host, bacterial, and environmental factors acting at gastric mucosa, that lead to the deregulation of many oncogenic signaling pathways[24]. Among them, the Wnt/β-catenin pathway is observed active in 30% to 50% of gastric cancer tissues and in several types of gastric cancer cell lines[25-27].

Available data confirmed that gain-of-function mutations in Wnt activators, as *CTNNB1* (the gene that encodes β-catenin protein), and/or inactivating mutations and promoter hypermethylation in tumor suppressor genes (*e.g.*, *APC*) lead to nuclear β-catenin accumulation and constitutive activation of the Wnt pathway in gastric cancer[11]. In the nucleus, free β-catenin binds TCF7L2 transcription factors, thereby modulating expression of genes (*e.g.*, *c-myc*) implicated in proliferation, inhibition of apoptosis, tissue invasion and metastasis[28]. It is known that alterations in *TCF7L2* gene and its expression, which also have a role in T2DM susceptibility, mediate carcinogenic effects through increased expression of *c-myc* and *cyclin D*[12,29]. Moreover, while several mutations in Wnt pathway components, such as *APC*, *CTNNB1*, *β-TrCP*, *Axin1* and *Axin2* have been implicated in gastric cancer[11,30], the only *TCF7L2* alterations so far reported in gastric tumors are somatic frameshift mutations in the exon 14 of the gene[31,32].

In our work the rs7903146 TT genotype was related with the risk of gastric cancer in the codominant and recessive models (OR = 3.61 and 3.11, respectively). Interestingly, the T allele at rs7903146 *TCF7L2* is the most correlated genetic variant with T2DM susceptibility, which has also been associated with the risk for several types of cancer.

Although, case-control studies involving *TCF7L2* rs7903146 and rs12255372 polymorphisms and cancer susceptibility have shown contradictory results, recent meta-analyses revealed that the *TCF7L2* rs7903146 SNP is associated significantly with the risk of breast, prostate and colon cancer, as well as between the rs12255372 polymorphism and the susceptibility of breast cancer[33-36]. Moreover, the rs12255372 SNP was not found associated with gastric cancer risk in this work.

The mechanism involving *TCF7L2* gene polymorphisms with cancer risk remains unclear, however the fact that *TCF7L2* gene product participates in Wnt/β-catenin signaling pathway allows to envisage their participation in carcinogenesis. Moreover, recent evidence suggests that *TCF7L2* polymorphisms may be related with changes in expression levels of its gene product. Gaulton *et al*[37] showed that the *TCF7L2* intronic SNP rs7903146 is located in an islet FAIRE (Formaldehyde-Assisted Isolation of Regulatory Elements)-enriched site and affects chromatin state and enhancer function. Furthermore, *TCF7L2* rs7094463, rs10749127, and rs11196224 SNPs, which correlate with recurrence of prostate cancer in patients that were treated with radical prostatectomy, are located in potential transcriptional regulatory regions[38]. It is suggested that these DNA polymorphisms can alter the transcription factor binding sites and thus affect the *TCF7L2* expression level.

Our results also suggest that the rs7903146 polymorphism (T allele) may be involved in defining the degree of differentiation of tumor cells. However, we cannot rule out that the small number of gastric adenocarcinoma samples with the *TCF7L2* rs7903146 TT genotype could drive the observed association with the degree of differentiation of tumor cells when it was used codominant and recessive models. The association of genetic and epigenetic alterations with subtypes of gastric carcinoma suggests particular interactions for the development of a gastric tumor with specific degree of differentiation[39-41]. Furthermore, due to the aggressiveness of gastric cancer has been associated with the degree of differentiation of tumor cells, the evaluation of this aspect should be considered in the management of gastric cancer[22,42].

In conclusion, this is the first study that examines the role of *TCF7L2* rs7903146 and rs12255372 SNPs related to susceptibility of gastric cancer in a Venezuelan high-risk population. Moreover, after adjustment for age and gender, we found that the rs7903146 polymorphism was significantly associated with the genetic susceptibility to gastric cancer in the Venezuelan population. This work gives additional support to understanding the participation of alterations in the Wnt/β-catenin pathway in the gastric carcinogenesis, and could represent a contribution to the identification of novel biomarkers for detection and/or monitoring progression or recurrence of gastric cancer. However, although the post-hoc analysis indicates that there was enough statistical power to support the observed associations, analysis of a larger sample size is needed to corroborate the participation of the *TCF7L2* polymorphisms in the risk of gastric cancer.

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COMMENTS

Background

TCF7L2 is an effector of the Wnt/β-catenin signaling pathway, whose deregulation can result in human carcinogenesis. *TCF7L2* variants rs12255372 and rs7903146 besides being associated with risk of type 2 diabetes have been involved in the development of several cancers.

Research frontiers

Gastric cancer continues being one of the leading causes of cancer-related death in the world. *TCF7L2* variants rs12255372 and rs7903146 have been

related to the development of some types of cancer, but their participation in the susceptibility of gastric cancer has not been evaluated yet.

Innovations and breakthroughs

Its results indicate that the rs7903146 T allele is associated with gastric cancer risk in Venezuelan population, suggesting its use as potential diagnosis biomarker in patients with this malignance.

Applications

Potential use of rs7903146 as diagnosis biomarker in patients with this gastric cancer.

Peer-review

The paper is well organized and the results are very straightforward and clear.

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